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EXAMINER	
STEELE, AMBER D	

ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 11/10/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/710,444	RIECHMANN ET AL.	
	Examiner	Art Unit	
	Amber D. Steele	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 September 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) *10 and 12* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,11 and 13-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9-26-05; 7-27-01*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The examiner for the current application has changed, however, the Technology Center (1600) and Art Unit (1639) have remained the same.

Status of the Claims

2. Claims 1-21 are currently pending.

Election/Restrictions

3. Applicant's species election without traverse of gene 3 of filamentous bacteriophage as the coat protein species and an antibody polypeptide as the heterologous polypeptide species in the reply filed on September 30, 2005 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

4. Newly submitted claims 10 and 12 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: Claim 1 is drawn to a method comprising (a) providing a virus encoding and displaying a fusion polypeptide which comprises a polypeptide, a viral coat protein, and a cleavable site, (b) exposing the virus to a cleaving agent, (c) propagating the virus comprising intact fusion protein. However, claim 10 states that members of the repertoire of phage displayed fusion proteins are partially unfolded and therefore susceptible to cleavage. The Specification clearly teaches that "the cleavable site is advantageously located in or adjacent to the heterologous polypeptide such that it can be protected by folding of the heterologous polypeptide and thus allow selection for heterologous polypeptides which are capable of correct folding" (please refer to page 6, lines 20-22). The Specification also clearly states that the fusion polypeptide "if cleaved will result in the

impairment of infectivity" (please refer to page 9, lines 19-20). Therefore, the partially unfolded fusion polypeptide of present claim 10 can not be propagated and does not comprise intact fusion protein (please refer to present claim 1). Moreover, claim 12 states that the exposing step (i.e. step (b) of present claim1) is undertaken in the presence of a protein denaturant. The presence of a protein denaturant would cause the protein to unfold and be susceptible to cleavage. Therefore, the unfolded fusion polypeptide of present claim 12 would be cleaved and no longer be "intact" and could not be propagated.

This invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 10 and 12 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Priority

5. Acknowledgment is made of applicant's claim for foreign priority based on the three applications filed in the United Kingdom on May 13, 1999 and May 13, 1998. It is noted, however, that applicant has not filed a certified copy of the PCT/GB99/01526, 9810223.9, or 9810228.8 applications as required by 35 U.S.C. 119(b).

6. Acknowledgment is made of applicant's claim for priority under 35 U.S.C. 119(a)-(d) based upon an application filed in the United Kingdom on May 13, 1998 (Application number 9810228.8). A claim for priority under 35 U.S.C. 119(a)-(d) cannot be based on said application, since the United States application was filed more than twelve months thereafter.

7. Acknowledgment is made of applicant's claim for priority under 35 U.S.C. 119(a)-(d) based upon an application filed in the United Kingdom on May 13, 1998 (Application number

9810223.9). A claim for priority under 35 U.S.C. 119(a)-(d) cannot be based on said application, since the United States application was filed more than twelve months thereafter.

8. Acknowledgment is made of applicant's claim for priority under 35 U.S.C. 119(a)-(d) based upon an application filed in the United Kingdom on May 13, 1999 (Application number PCT/GB99/01526). A claim for priority under 35 U.S.C. 119(a)-(d) cannot be based on said application, since the United States application was filed more than twelve months thereafter.

Oath/Declaration

9. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:
Non-initialed and/or non-dated alterations have been made to the oath or declaration. See 37 CFR 1.52(c).

The declaration states that "this declaration is for a national stage of PCT application", however, the current application is not a 371. Appropriate correction is required.

The declaration states that the country of citizenship is "French" or "British" which are not countries, but nationalities. Appropriate correction is required.

Specification

10. The following guidelines illustrate the preferred layout for the specification of a utility application. These guidelines are suggested for the applicant's use.

Arrangement of the Specification

As provided in 37 CFR 1.77(b), the specification of a utility application should include the following sections in order. Each of the lettered items should appear in upper case, without underlining or bold type, as a section heading. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

(a) TITLE OF THE INVENTION.
(b) CROSS-REFERENCE TO RELATED APPLICATIONS.

(c) STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT.
(d) THE NAMES OF THE PARTIES TO A JOINT RESEARCH AGREEMENT
(e) INCORPORATION-BY-REFERENCE OF MATERIAL SUBMITTED ON A COMPACT DISC (See 37 CFR 1.52(e)(5) and MPEP 608.05. Computer program listings (37 CFR 1.96(c)), "Sequence Listings" (37 CFR 1.821(c)), and tables having more than 50 pages of text are permitted to be submitted on compact discs.) or
REFERENCE TO A "MICROFICHE APPENDIX" (See MPEP § 608.05(a). "Microfiche Appendices" were accepted by the Office until March 1, 2001.)
(f) BACKGROUND OF THE INVENTION.
(1) Field of the Invention.
(2) Description of Related Art including information disclosed under 37 CFR 1.97 and 1.98.
(g) BRIEF SUMMARY OF THE INVENTION.
(h) BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWING(S).
(i) DETAILED DESCRIPTION OF THE INVENTION.
(j) CLAIM OR CLAIMS (commencing on a separate sheet).
(k) ABSTRACT OF THE DISCLOSURE (commencing on a separate sheet).
(l) SEQUENCE LISTING (See MPEP § 2424 and 37 CFR 1.821-1.825. A "Sequence Listing" is required on paper if the application discloses a nucleotide or amino acid sequence as defined in 37 CFR 1.821(a) and if the required "Sequence Listing" is not submitted as an electronic document on compact disc).

11. The disclosure is objected to because of the following informalities:

a. On page 9, line 25 the phrase "the viral will" appears to be a typographical error. The phrase "the virus will" is suggested.

b. On page 12, line 32 the phrase "cleavable site on to near to an associated tag" appears to be a typographical error.

c. The full name for the abbreviation GndHCl should appear with the first use of the abbreviation. The full name first appears on page 27, line 2, but the abbreviation is first used on page 15, line 1.

d. On page 17, Table 1 the art-accepted abbreviation for the potential of Hydrogen is pH not PH.

e. On page 18, line 10 the phrase "express fusion protein" appears to be a typographical error. The phrase "expressed fusion protein" is suggested.

f. On page 37, line 25 "a^{32}P-dCTP" appears to be a typographical error. Either the use of the symbol alpha or writing out the word alpha is suggested.

g. On page 39, the original page is skewed and text is missing from the right margin of Table 8 and lines 29-31. The amendment received on July 30, 2002 corrected the missing text for lines 17-27.

h. On page 40, line 4 the amino acid sequence "AGGAAA" does not have a corresponding SEQ ID NO. In addition, the sequence listing does not appear to reference the amino acid sequence "AGGAAA".

i. While the abbreviations pIII, p3, g3, gIII, gene 3, and gene III for coat protein III (protein or nucleic acid) are well known in the art, the use of several different abbreviations for the same term in one application is somewhat confusing. A definition of the coat protein with appropriate abbreviations would clarify the issue.

Appropriate correction is required.

12. The use of the trademarks Pefabloc, Sculptor, and ECL have been noted in this application. The trademarks should be capitalized wherever the trademarks appear and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim Objections

13. Claim 2 is objected to because of the following informalities: The phrase "in wherein the cleavage site" appears to be a typographical error. Appropriate correction is required.

Claim Rejections - 35 USC § 112

14. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

15. Claims 1 and all dependent claims thereof are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant is directed to the Guidelines for the Examination of Patent Applications under the 35 USC 112, first paragraph "Written Description" requirement, Federal Register, Vol. 66, No. 4 pages 1099-1111, Friday January 5, 2001. This is a **written description** rejection.

16. Claim 1 is drawn to a method for the selection of a virus comprising (a) providing a virus encoding and displaying a fusion polypeptide comprising a polypeptide and a viral coat protein with a cleavable site, (b) exposing the virus to a cleaving agent, and (c) propagating the virus comprising intact fusion protein. The invention as claimed encompasses all known polypeptides and all potential fusion polypeptides since virtually any polypeptide can be cleaved under proper conditions by proteases (e.g. present claim 21) and therefore comprises a cleavable site. The claimed invention states that a fusion polypeptide with a cleavable site will be exposed to a

cleaving agent and then an **intact** fusion polypeptide will be propagated. The claimed invention does not include any structural information regarding the fusion polypeptide except that the fusion polypeptide contains a cleavable site. In addition, the claimed invention does not include any structural information regarding how a displayed polypeptide comprising a cleavable site would be exposed to a cleaving agent and still remain intact. The structural limitation that the fusion polypeptide must be properly folded in order for propagation of virus comprising intact fusion protein is not present in the claimed invention. Furthermore, the specification does not teach how virus exposed to a cleaving agent could be propagated. Is the virus resistant to cleavage by the cleaving agent? Can the virus actually propagate after exposure to the cleaving agent?

The Specification clearly teaches that "the cleavable site is advantageously located in or adjacent to the heterologous polypeptide such that it can be protected by folding of the heterologous polypeptide and thus allow selection for heterologous polypeptides which are capable of correct folding" (please refer to page 6, lines 20-22). In addition, the specification also teaches that "protease cleavage sites may be incorporated into the coat protein of a virus by constructing a fusion between the coat protein and a further polypeptide, the further polypeptide containing the cleavage site" and "the further polypeptide should be inserted at a position in the viral coat protein such that it allows the assembly of a functional viral capsid and subsequenct infection, but if cleaved will result in the impairment of infectivity" (please refer to page 9, lines 15-20). However, the claimed invention does not include the structural limitation that the fusion polypeptide must be properly folded in order for propagation of virus comprising intact fusion protein. Furthermore, the specification does not teach how cleaved virus could be propagated.

Therefore, one skilled in the relevant art would not reasonably conclude that the Applicants had possession of the invention as claimed since the structural limitation of the fusion polypeptide being sufficiently folded to protect the polypeptide from cleavage is not included in the claimed invention.

17. Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was *in possession of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See page 1116.).

With the exception of providing a virus displaying a polypeptide correctly folded to protect from cleavage as disclosed by the specification, the skilled artisan cannot envision the method of claim 1. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class wherein the specification provided only the bovine sequence.

18. Claim 4 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described

in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant is directed to the Guidelines for the Examination of Patent Applications under the 35 USC 112, first paragraph "Written Description" requirement, Federal Register, Vol. 66, No. 4 pages 1099-1111, Friday January 5, 2001. This is a **written description** rejection.

19. Claim 1 is drawn to a method for the selection of a virus comprising (a) providing a virus encoding and displaying a fusion polypeptide comprising a polypeptide and a viral coat protein with a cleavable site, (b) exposing the virus to a cleaving agent, and (c) propagating the virus comprising intact fusion protein. Claim 4 is drawn to "the method according to claim 1 wherein cleavage impairs the ability of the polypeptide comprising the cleavage site to mediate the infection of the virus". Therefore, viral infection is impaired and an intact fusion polypeptide can not be propagated unless the virus expressing intact fusion polupeptide is somehow protected from cleavage. In addition, how a polypeptide can mediate infection of a virus is not adequately described.

The Specification does not describe how to "propagate a virus comprising intact fusion protein" (e.g. present claim 1) "after cleavage of the virus which impairs infection of the virus". No examples are provided in the Specification where a fusion polypeptide is cleaved and then propagated to produce an intact fusion polypeptide. However, the Specification does describe that "the polypeptide should be inserted at a position in the viral coat protein such that it allows the assembly of a functional viral capsid and subsequenct infection, but if cleaved will result in the impairment of infectivity" (please refer to page 9, lines 15-20). The structural limitation that a properly folded fusion polypeptide would prevent cleavage of the polypeptide and allow a virus

exposed to a cleaving agent to propagate an intact fusion polypepotide is not provided in the claimed invention. Furthermore, the limitation of claim 4 renders step (c) of claim 1 unfeasible.

In addition, the Specification does not describe how a polypeptide can "mediate the infection of the virus". There are no examples in the specification of a polypeptide mediating infection of a virus. The Specification does describe how to mediate infection of a host cell by the virus (please refer to page 14, lines 27-28), but not how to mediate infection of the virus. Furthermore, the Specification describes how infectivity of the virus is altered by cleavage (please refer to page 8, lines 13-21). Therefore, one of skill in the art would not reasonably conclude that the Applicants had possession of the invention as claimed since mediating infection of the virus or propagating virus with intact fusion polypeptides after cleavage is not described.

20. Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was *in possession of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See page 1116.).

With the exception of cleavage rendering any phage not containing a fusion polypeptide noninfectious (e.g. background phage are noninfectious) as disclosed by the specification, the skilled artisan cannot envision the method of claim 1. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V.

Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

21. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

22. Claims 1 and all dependent claims thereof are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: Selecting virus which are resistant to cleavage (please refer to page 7, line 16 of the Specification). A selection step between steps (b) and (c) of the presently claimed invention is necessary since only properly folded fusion polypeptides would be protected from cleavage and thus allow propagation of virus encoding an intact fusion polypeptide. Fusion polypeptides that were not protected from cleavage during the exposure step would be cleaved and therefore no longer be intact.

23. Claims 1 and 2 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The limitation of claim 1 stating that "a cleavable site located within a displayed polypeptide" and the limitation of claim 2 stating that "the cleavable site is located within the fusion polypeptide" are indefinite. The phrases are indefinite because it is not clear if the cleavable site should only be in the displayed portion of the polypeptide or if the cleavable site can be anywhere in the fusion polypeptide including non-displayed portions anchored in the phage capsid. Therefore, claims 1 and 2 are indefinite.

24. Claim 4 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The terms "impairs" and "mediate" in claim 4 are relative terms which render the claim indefinite. The terms "impairs" or "mediate" are not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The limitation of claim 4 stating that "cleavage **impairs** the ability of the polypeptide...to **mediate** the infection of the virus" is not clear because it in unknown how a polypeptide "**mediates**" infection of a virus. Does the polypeptide enhance or decrease infection, is it suggested that the polypeptide actually infects the virus (if so, how?), or is the actual infectivity of virus being altered? Furthermore, does "**impairs**" mean that infection is decreased 10%, 20%, 40%, 80%, etc.

25. Claims 19 and 20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The limitation of claim 19 stating that "the bacteriophage is a helper bacteriophage used in conjunction with phagemids" and the limitation of claim 20 stating that "the encapsidated nucleic acid of the bacteriophage is a phagemid and requires the used of a helper bacteriophage" are indefinite. The phrases are indefinite because it is not clear if two bacteriophage are present (e.g. one carrying the phagemid and one helper phage), if the helper phage is carrying the phagemid, a replication deficient bacteriophage carries the phagemid and a "packaging" helper phage is required to package more phagemid nucleic acid, or if the host cell is transfected with the phagemid, infected with a "packaging" helper phage, and then the helper

phage encapsidates the phagemid nucleic acid, etc. Therefore, the limitations of claims 19 and 20 are indefinite.

26. Claim 2 recites the limitation "the **cleavage** site" in the first line of claim 2. There is insufficient antecedent basis for this limitation in the claim because claim 1 recites a "cleavable site". "Cleavage site" suggests that cleavage has occurred (e.g. the act of cleaving) while "cleavable site" suggests the property of being able to be cleaved only (e.g. capable of being cleaved).

27. Claim 3 recites the limitation "cleaved or uncleaved fusion polypeptide" in line 2 of claim 3. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 102

28. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

29. The presently claimed invention is directed to:

A method for the selection of a virus comprising:

a. providing a virus
b. exposing the virus to a cleaving agent
c. propagating the virus

30. Claims 1-9, 11, 13-17, and 19-21 are rejected under 35 U.S.C. 102(b) as being anticipated by Ladner *et al.* U.S. patent 5,223,409 issued June 29, 1993.

Ladner *et al.* teach phage-displayed binding proteins (please refer to Abstract). Ladner *et al.* also teach a method comprising (a) preparing a variegated population of amplifiable genetic packages expressing a chimeric protein comprising a potential binding domain and an outer surface transport signal, (b) causing expression of the chimeric protein on the outer surface of the genetic packages, (c) contacting the packages with a target (e.g. ligand of present claims 13 and 15), (d) recovering and replicating at least one package bearing a successful binding domain (e.g. providing a virus, exposing the virus to a cleaving agent, and propagating the virus of present claim 1; please refer to column 10, lines 14-37). In addition, Ladner *et al.* teach that the chimeric protein contains a flexible linker which can form the recognition site for a specific protease and the target can be a protease (e.g. cleavable site of present claims 1-2, 7, and 21 and a protease of claim 21; please refer to column 57, lines 38-57, column 73, lines 21-40, column 88, lines 2-3, column 89, lines 40-65, column 104, lines 41-57). Additionally, Ladner *et al.* teach that the genetic package is a filamentous phage and the DNA encoding a potential binding domain is linked to gene III to form a chimeric protein (e.g. polypeptide and viral coat protein of present claim 1, bacteriophage of present claim 16, and gene 3 of present claim 17; please refer to column 51, lines 10-68). Ladner *et al.* also teach that the potential binding domain can be an antibody but is not limited to antibodies (please refer to column 15, lines 23-68 and column 16, lines 1-34). Ladner *et al.* further teach that the genetic packages displaying chimeric proteins can be proteolytically cleaved and separated or selected (e.g. present claim 3; please refer to column 73, lines 21-40, column 93, lines 10-44, column 98, lines 23-68, and column 99, lines 1-17). Furthermore, Ladner *et al.* teach that the selected phage-displayed chimeric proteins can be amplified by infection of a host cell (please refer to column 99, lines 19-25). Moreover, Ladner *et al.* teach that the protease cleavage can alter bacteriophage titer (e.g. cleavage impairs infection of present claim 4, cleavage resistance can be propagated by infection of present claim 8, and present claim 9; please refer to column 117, lines 38-68 and column 118, lines 1-50).

Ladner *et al.* further teach the production of a population of genetic packages displaying a multitude of different potential binding domains on the surface (e.g. repertoire of sequences of present claims 5-7; please refer to column 8, lines 1-50). Ladner *et al.* teach that polypeptides may be folded and stabilize into a particular conformation, however, a denaturing agent can be added to perturb the conformational folding of the polypeptide (e.g. molecule which stabilizes or

destabilizes of present claim 11; please refer to column 25, lines 60-68 and column 26, lines 1-12). In addition, Ladner *et al.* teach that the folded conformation of the polypeptide can alter the ability of proteases to degrade the polypeptide (please refer to column 26, lines 50-53). Furthermore, Ladner *et al.* teach that any ions or cofactors known to be essential for the stability of the protein binding domain can be added to the genetic packages during testing or target binding (e.g. present claim 14; please refer to column 77, lines 50-66). Ladner *et al.* also teach that proteins can be expressed on the surface of phage by being inserted in the gene III protein (please refer to column 5, lines 23-43). In addition, Ladner *et al.* teach that the protein domain of the chimeric protein can be expressed as a domain of gene III or fused to gene III at the site used by Smith (e.g. second and third domain of gene 3 of present claim 18), at a codon corresponding to another domain boundary, the surface loop, or the amino terminus of gene III (please refer to column 58, lines 1-58, column 70, lines 43-68, column 71, lines 1-68, and column 72, lines 1-33). Ladner *et al.* teach that phagemids in combination with phages can be utilized to display the chimeric proteins on the phage (e.g. present claims 19-20; please refer to column 76, lines 15-68 and column 77, lines 1-19). Overall, a person of ordinary skill in the art would have anticipated the presently claimed invention of claims 1-9, 11, and 13-21 in view of Ladner *et al.*

31. Claims 1-3, 5-7, 11, 13-17, and 21 are rejected under 35 U.S.C. 102(b) as being anticipated by Dower *et al.* U.S. Patent 5, 432, 018 issued July 11, 1995.

Dower *et al.* teach screening and selecting bacteriophage expressing fusion proteins comprising peptides and coat proteins (e.g. bacteriophage of present claim 16; please refer to the Abstract and column 3, lines 49-62). Dower *et al.* claim a method for obtaining a bacteriophage encoding a substrate cleaved by a proteolytic enzyme comprising (a) transforming host cells with bacteriophage expression vectors encoding a fusion protein composed of a peptide fused to a ligand fused to a coat protein of filamentous bacteriophage, (b) cultivating the host cells suitable for expression and assembly of bacteriophage, (c) incubating the bacteriophage with a proteolytic enzyme wherein the displayed peptide is cleavable by the proteolytic enzyme, (d) contacting the bacteriophage to a receptor that binds the ligand, and (e) separating receptor-bound bacteriophage from unbound bacteriophage (e.g. providing a virus, exposing the virus to a

cleaving agent, propagating virus comprising intact fusion protein of present claim 1, cleavage site located in the fusio polypeptide of present claim 2, separating virus expressing uncleaved and cleaved polypeptides of present claim 3, presence of a stabilizer of present claim 11, presence of ligand of present claim 13, selected by binding ligand of present claim 15, and a protease cleavable site of present claim 21; please refer to claims 1-2 of Dower *et al.*). Dower *et al.* also claim the coat protein of fd filamentous bacteriophage pIII (e.g. gene 3 of filamentous bacteriophage of present claim 17; please refer to claim 7 of Dower *et al.*). Dower *et al.* teach library construction of peptide-phage libraries comprising specifying the enzyme substrate recognition site within or adjacent to the variable nucleotide region of the library so most members of the library are modified (e.g. repertoire of sequences of present claims 5-7; please refer to columns 5-12, particularly column 11, lines 2-9). In addition, Dower *et al.* teach peptide-phage libraries with protease cleavage sites (e.g. displayed heterologous peptide with a cleavable site of present claims 6-7; please refer to column 12, lines 62-68 and column 13, lines 1-17). Additionally, Dower *et al.* teach that phages which express peptides without the desired specificity are removed by washing and selection of peptides within a particular range of affinity for the receptor (e.g. isolation of a protein with improved stability of present claim 14; please refer to column 14, lines 16-37). Overall, a person of ordinary skill in the art would have anticipated the presently claimed invention of claims 1-3, 5-7, 11, 13-17, and 21 in view of Dower *et al.*

Claim Rejections - 35 USC § 103

32. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

33. Claims 1-9, 11, and 13-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ladner *et al.* U.S. patent 5,223,409 issued June 29, 1993 and Smith, G. P. Science. Filamentous

Fusion Phage: Novel Expression Vectors that Display Cloned Antigens on the Virion Surface. 228: 1315-1317, 1985.

34. Ladner *et al.* teach phage-displayed binding proteins (please refer to Abstract). Ladner *et al.* teach a method comprising (a) preparing a variegated population of amplifiable genetic packages expressing a chimeric protein comprising a potential binding domain and an outer surface transport signal, (b) causing expression of the chimeric protein on the outer surface of the genetic packages, (c) contacting the packages with a target (e.g. ligand of present claims 13 and 15), (d) recovering and replicating at least one package bearing a successful binding domain (e.g. providing a virus, exposing the virus to a cleaving agent, and propagating the virus of present claim 1; please refer to column 10, lines 14-37). In addition, Ladner *et al.* teach that the chimeric protein contains a flexible linker which can form the recognition site for a specific protease and the target can be a protease (e.g. cleavable site of present claims 1-2, 7, and 21 and a protease of claim 21; please refer to column 57, lines 38-57, column 73, lines 21-40, column 88, lines 2-3, column 89, lines 40-65, column 104, lines 41-57). Additionally, Ladner *et al.* teach that the genetic package is a filamentous phage and the DNA encoding a potential binding domain is linked to gene III (e.g. polypeptide and viral coat protein of present claim 1, bacteriophage of present claim 16, and gene 3 of present claim 17; please refer to column 51, lines 10-68). Ladner *et al.* also teach that the potential binding domain can be an antibody but is not limited to antibodies (please refer to column 15, lines 23-68 and column 16, lines 1-34). Ladner *et al.* further teach that the genetic packages displaying chimeric protein can be proteolytically cleaved and separated (e.g. present claim 3; please refer to column 73, lines 21-40, column 93, lines 10-44, column 98, lines 23-68, and column 99, lines 1-17). Furthermore, Ladner *et al.* teach that the selected phage-displayed chimeric proteins can be amplified by infection of a host cell (please refer to column 99, lines 19-25). Moreover, Ladner *et al.* teach that the protease cleavage can alter bacteriophage titer (e.g. cleavage impairs infection of present claim 4, cleavage resistance can be propagated by infection of present claim 8, and present claim 9; please refer to column 117, lines 38-68 and column 118, lines 1-50). Ladner *et al.* teach the production of a population of genetic packages displaying a multitude of different potential binding domains on the surface (e.g. repertoire of sequences of present claims 5-7; please refer to column 8, lines 1-50). Ladner

et al. teach that polypeptides may be folded and stabilize into a particular conformation, however, a denaturing agent can be added to perturb the conformational folding of the polypeptide (e.g. molecule which stabilizes or destabilizes of present claim 11; please refer to column 25, lines 60-68 and column 26, lines 1-12). In addition, Ladner *et al.* teach that the folded conformation of the polypeptide can alter the ability of proteases to degrade the polypeptide (please refer to column 26, lines 50-53). Furthermore, Ladner *et al.* teach that any ions or cofactors known to be essential for the stability of the protein binding domain can be added to the genetic packages during testing or target binding (e.g. present claim 14; please refer to column 77, lines 50-66). Ladner *et al.* teach that proteins can be expressed on the surface of phage by being inserted in the gene III protein (please refer to column 5, lines 23-43). Furthermore, Ladner *et al.* teach that the protein domain of the chimeric protein can be expressed as a domain of gene III or fused to gene III at the site used by Smith (e.g. second and third domain of gene 3 of present claim 18), at a codon corresponding to another domain boundary, the surface loop, or the amino terminus of gene III (please refer to column 58, lines 1-58, column 70, lines 43-68, column 71, lines 1-68, and column 72, lines 1-33). Ladner *et al.* teach that phagemids and helper phages can be utilized to display the chimeric proteins on the phage (e.g. present claims 19-20; please refer to column 76, lines 15-68 and column 77, lines 1-19).

However, while Ladner *et al.* teach that the protein binding domain can be fused to gene III at the site used by Smith, Ladner *et al.* does not specifically describe the site used by Smith as the second and third domain of gene 3.

Smith teaches that a foreign sequence can be inserted between the F pilus binding domain and the domain that is buried in the virion of pIII without disrupting pIII function (e.g. second and third domains of gene 3 of present claim 18; please refer to page 1315).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the teaching of Ladner *et al.* with the specific location of the peptide between the second and third domains of the pIII coat protein taught by Smith.

One having ordinary skill in the art would have been motivated to do this because the insertion of a sequence between the second and third domains of pIII did not disrupt pIII function (please refer to Smith page 1315, first column and Figure1). Furthermore, the location of the peptide and pIII in the fusion polypeptide would be a design choice as long as the fusion polypeptide would be functional.

There is a reasonable expectation of success in the combination of Ladner *et al.* and Smith because of the data in Figure 1 of Smith showing that a sequence can be inserted between the second and third domains of pIII wherein pIII is still functional. In addition, Ladner *et al.* specifically references Smith (please refer to column 58, lines 38-45).

Therefore, the combination of Ladner *et al.* and Smith renders the instant claims 1-9, 11, and 13-21 *prima facie* obvious.

35. Claims 1-3, 5-7, 11, 13-17, and 19-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dower *et al.* U.S. Patent 5, 432, 018 issued July 11, 1995 and Breitling *et al.* U.S. Patent 5,849,500 issued December 15, 1998.

36. Dower *et al.* teach screening and selecting bacteriophage expressing fusion proteins comprising peptides and coat proteins (e.g. bacteriophage of present claim 16; please refer to the Abstract and column 3, lines 49-62). Dower *et al.* claim a method for obtaining a bacteriophage encoding a substrate cleaved by a proteolytic enzyme comprising (a) transforming host cells with bacteriophage expression vectors encoding a fusion protein composed of a peptide fused to a ligand fused to a coat protein of filamentous bacteriophage, (b) cultivating the host cells suitable for expression and assembly of bacteriophage, (c) incubating the bacteriophage with a

proteolytic enzyme wherein the displayed peptide is cleavable by the proteolytic enzyme, (d) contacting the bacteriophage to a receptor that binds the ligand, and (e) separating receptor-bound bacteriophage from unbound bacteriophage (e.g. providing a virus, exposing the virus to a cleaving agent, propagating virus comprising intact fusion protein of present claim 1, cleavage site located in the fusio polypeptide of present claim 2, separating virus expressing uncleaved and cleaved polypeptides of present claim 3, presence of a stabilizer of present claim 11, presence of ligand of present claim 13, selected by binding ligand of present claim 15, and a protease cleavable site of present claim 21; please refer to claims 1-2 of Dower *et al.*). Dower *et al.* also claim the coat protein of fd filamentous bacteriophage pIII (e.g. gene 3 of filamentous bacteriophage of present claim 17; please refer to claim 7 of Dower *et al.*). Dower *et al.* teach library construction of peptide-phage libraries comprising specifying the enzyme substrate recognition site within or adjacent to the variable nucleotide region of the library so most members of the library are modified (e.g. repertoire of sequences of present claims 5-7; please refer to columns 5-12, particularly column 11, lines 2-9). In addition, Dower *et al.* teach peptide-phage libraries with protease cleavage sites (e.g. displayed heterologous peptide with a cleavable site of present claims 6-7; please refer to column 12, lines 62-68 and column 13, lines 1-17). Additionally, Dower *et al.* teach that phages which express peptides without the desired specificity are removed by washing and selection of peptides within a particular range of affinity for the receptor (e.g. isolation of a protein with improved stability of present claim 14; please refer to column 14, lines 16-37).

However, Dower *et al.* does not teach the use of phagemid and helper bacteriophage.

Breitling *et al.* teach a phagemid that expresses an antibody fused to pIII protein wherein the phagemid is suitable for selecting specific antibodies from large gene libraries (please refer to the Abstract). Breitling *et al.* also teach that peptides can be inserted between two domains of pIII (please refer to column 1, lines 43-51). Breitling *et al.* further teach the use of the phagemid pSEX and the phage fd to express the antibody-pIII fusion protein (please refer to column 4, lines 55-64). In addition, Breitling *et al.* teach the use of a protease cleavage site (please refer to column 3, lines 17-20).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the phage-displayed library of Dower *et al.* with the antibody-pIII fusion protein expressed by phagemid with a helper phage of Breitling *et al.*

One having ordinary skill in the art would have been motivated to do this because Breitling *et al.* teach that larger inserts have an adverse effect on the infectivity function of pIII and there is a risk that phage libraries will become dominated by deletion mutants after library amplification (please refer to column 2, lines 3-15). Furthermore, Breitling *et al.* teach that the phagemid is propagated as a plasmid and is not under selection pressure to remove antibody DNA (please refer to column 2, lines 19-36).

There is a reasonable expectation of success in the modification of the phage-displayed library of Dower *et al.* with the teachings of Breitling *et al.* because of the example in Breitling *et al.* showing the expression of antibody-pIII fusion protein from a phagemid with a helper bacteriophage (please refer to columns 3-5 and Figure 2 of Breitling *et al.*).

Therefore, the combination of the teachings of Dower *et al.* and Breitling *et al.* render the instant claims 1-3, 5-7, 11, 13-17, and 19-21 *prima facie* obvious.

37. Claim 18 is rejected under 35 U.S.C. 103(a) as being unpatentable over Dower *et al.* U.S. Patent 5, 432, 018 issued July 11, 1995 and Breitling *et al* U.S. Patent 5,849,500 issued December 15, 1998 as applied to claims 1-3, 5-7, 11, 13-17, and 19-21 above, and further in view of Smith, G. P. Science. Filamentous Fusion Phage: Novel Expression Vectors that Display Cloned Antigens on the Virion Surface. 228: 1315-1317, 1985.

The combine teachings of Dower *et al.* and Breitling *et al.* are obvious over the presently claimed invention since it is obvious to utilize phagemids for expressing large polypeptides on the surface of phage as discussed in section 36 above. However, the combine teachings of Dower *et al.* and Breitling *et al.* differ from the presently claimed invention by failing to the insertion of the polypeptide between the second and third domains of gene 3.

Smith teaches that a foreign sequence can be inserted between the F pilus binding domain and the domain that is buried in the virion without disrupting pIII function (e.g. second and third domains of gene 3 of present claim 18; please refer to page 1315).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the teachings of the bacteriophage-displayed fusion polypeptides of Dower *et al.* and Breitling *et al.* with the specific location of the peptide between the second and third domains of the pIII coat protein taught by Smith.

One having ordinary skill in the art would have been motivated to do this because the insertion of a sequence between the second and third domains of pIII did not disrupt pIII function (please refer to Smith page 1315, first column and Figure1). Furthermore, the location of the peptide and pIII in the fusion polypeptide would be a design choice if the fusion polypeptide would be functional.

There is a reasonable expectation of success in the combination of Dower *et al.*, Breitling *et al.*, and Smith because of the data in Figure 1 of Smith showing that a sequence can be inserted between the second and third domains of pIII wherein pIII is still functional.

Therefore, the combination of Dower *et al.*, Breitling *et al.*, and Smith renders the instant claims 1-3, 5-7, 11, and 13-21 *prima facie* obvious.

38. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amber D. Steele whose telephone number is 571-272-5538. The examiner can normally be reached Monday through Friday 9:00AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

ADS
November 4, 2005

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